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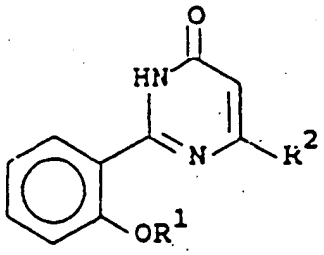
(54) Chemical compounds.

(57) Compounds of the formula (1):



(1)

and pharmaceutically acceptable salts thereof are described wherein R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-6}alkyl, phenylC_{1-6}alkyl or C_{1-6}alkyl substituted by 1 to 6 fluoro groups; and R^2 is C_{1-6}alkyl, phenyl, hydroxy, C_{1-6}alkoxy, halo, $-NHCOR^3$, $-NHCONHR^4$, 5-tetrazolyl, $-CO_2R^5$, cyano, $-CONR^6R^7$, or $-NR^8R^9$ wherein R^3 to R^7 are independently hydrogen or C_{1-6}alkyl and R^8 and R^9 are independently hydrogen or C_{1-6}alkyl optionally substituted by hydroxy provided that the carbon atom adjacent to the nitrogen atom is not substituted by hydroxy.

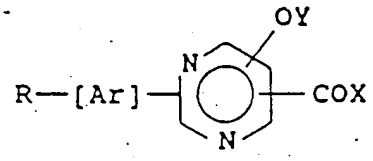
Processes for their preparation, pharmaceutical compositions comprising them and their use as medicaments are also described.

EP 0 395 328 A2

CHEMICAL COMPOUNDS

The present invention relates to phenylpyrimidone derivatives, processes for their preparation, their use as therapeutic agents and to pharmaceutical compositions containing them. The compounds of this invention are inhibitors of a calmodulin insensitive cyclic GMP phosphodiesterase and are of use in combatting such conditions where such inhibition is thought to be beneficial. They are bronchodilators and are therefore of use in combatting chronic reversible obstructive lung diseases such as asthma and bronchitis. Furthermore they are vasodilators and are therefore of value in combatting angina, hypertension and congestive heart failure. They are of use in the treatment of gastrointestinal motility disorders, for example irritable bowel syndrome.

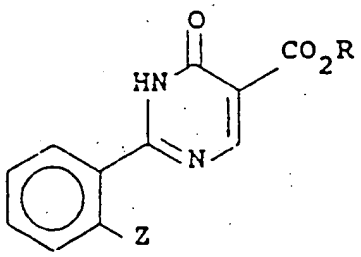
US Patents 3660403 and 3745161 disclose compounds of the general formula (A) :



(A)

wherein COX and OY are ortho to each other and [Ar] is para to either COX or OY, R is inter alia lower alkoxy, [Ar] is inter alia phenyl, X is inter alia hydroxy, amino, alkylamino, dialkylamino or alkoxy, and Y is inter alia hydrogen. These compounds are described as having anti-inflammatory, anti-pyretic and analgesic activity. None of the compounds of the present invention are specifically disclosed.

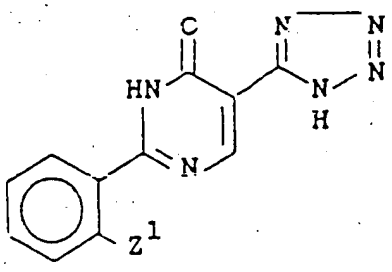
US Patent 4031093 discloses anti-allergic compounds of the formula (B) :



(B)

wherein Z is inter alia C_{2-5}alkoxy or C_{2-5}alkenyloxy and R is hydrogen or the residue of an easily cleavable ester group.

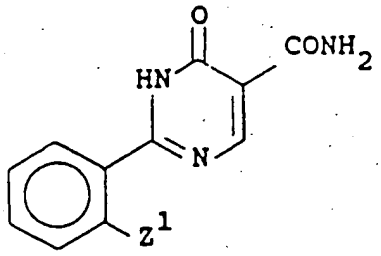
US Patent 4082751 discloses anti-allergic compounds of the formula (C) :



(C)

wherein Z^1 is inter alia lower alkoxy or lower alkenyloxy.

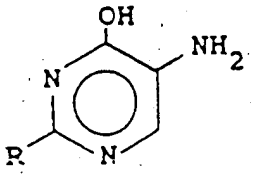
US Patent 4082751 also discloses intermediate compounds of the formula (D) :



(D)

wherein Z^1 is as hereinbefore defined. In J. Med. Chem. 1982, 25, 1145-1150 it is indicated at page 1148 that the compounds of the formula (D) have insignificant anti-allergic activity.

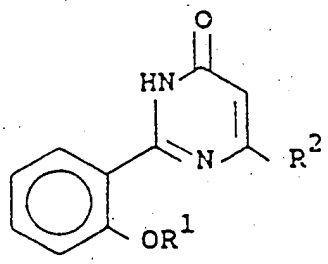
US Patent 4241056 discloses 3-(4-hydroxy-5-pyrimidyl)ureido-penicillins. As intermediates for such compounds are described compounds of the general formula (E) :



(E)

wherein R is inter alia phenyl optionally substituted by C_{1-6}alkoxy. None of the compounds of the present invention are specifically disclosed.

According to the present invention there is provided compounds of the formula (1) :



(1)

and pharmaceutically acceptable salts thereof, wherein

R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-6}alkyl, phenylC_{1-6}alkyl or C_{1-6}alkyl substituted by 1 to 6 fluoro groups; and

R^2 is C_{1-6}alkyl, phenyl, hydroxy, C_{1-6}alkoxy, halo, -NHCOR^3, -NHCONHR^4, 5-tetrazolyl, -CO_2R^5, cyano, -CONR^{6}R^7, or -NR^{8}R^9 wherein R^3 to R^7 are independently hydrogen or C_{1-6}alkyl and R^8 and R^9 are independently hydrogen or C_{1-6}alkyl optionally substituted by hydroxy provided that the carbon atom adjacent to the nitrogen atom is not substituted by hydroxy.

Suitably R^1 is C_{2-5}alkyl for example ethyl, n-propyl, isopropyl, butyl, isobutyl or pentyl.

Suitably R^1 is C_{3-5}alkenyl for example allyl, butenyl or pentenyl.

Suitably R^1 is cyclopropylmethyl or benzyl.

Examples of C_{1-6}alkyl substituted by 1 to 6 fluoro groups include -CF_3, -CH_2CF_3 or -CF_2CHFCF_3.

Preferably R^1 is n-propyl.

Suitably R^2 is phenyl or C_{1-6}alkyl for example methyl, ethyl, propyl or butyl.

Suitably R^2 is hydroxy, C_{1-6}alkoxy for example methoxy, ethoxy or propoxy, or halo for example fluoro, chloro, bromo or iodo.

Suitably R^2 is -NHCOR^3 for example formamido, acetamido, propionamido or butyramido.

Suitably R^2 is -NHCONHR^4 for example ureido or N-methylureido.

Suitably R^2 is 5-tetrazolyl or -CO_2R^5 for example carboxy, methoxycarbonyl or ethoxycarbonyl.

Suitably R^2 is cyano or -CONR^{6}R^7 for example carboxamido, N-methylcarboxamido, N-ethylcarboxamido or N-propylcarboxamido.

Suitably R^2 is -NR^{8}R^9 for example amino, methylamino, ethylamino, propylamino, 2-hydroxyethylamino,

3-hydroxypropylamino or bis-(2-hydroxyethyl)amino.

Specific compounds of this invention are :

6-amino-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-acetamido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-propionamido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-butyramido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-N'-methylureido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
4,6-dihydroxy-2-(2-propoxyphenyl)pyrimidine,
4-chloro-6-hydroxy-2-(2-propoxyphenyl)pyrimidine,
6-ethylamino-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-propylamino-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-(2-hydroxyethylamino)-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-(3-hydroxypropylamino)-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
4-hydroxy-6-methyl-2-(2-propoxyphenyl)pyrimidine,
6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxylic acid,
ethyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxylate,
6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
4-cyano-6-hydroxy-2-(2-propoxyphenyl)pyrimidine,
2-(2-propoxyphenyl)-6-(1H-tetrazol-5-yl)pyrimidin-4(3H)-one,
4-ethyl-6-hydroxy-2-(2-propoxyphenyl)pyrimidine,
4-hydroxy-6-phenyl-2-(2-propoxyphenyl)pyrimidine,
N-methyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
N-ethyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
N-propyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
6-ethoxy-2-(2-propoxyphenyl)pyrimidin-4(3H)-one, or
6-N,N-bis-(2-hydroxyethyl)amino-2-(2-propoxyphenyl)pyrimidin-4(3H)-one,
or pharmaceutically acceptable salts thereof.

This invention covers all tautomeric and optical isomeric forms of compounds of formula (1).

Compounds of the formula (1) wherein R^2 is $-NR^8R^9$ may form pharmaceutically acceptable salts with acids such as hydrochloric, hydrobromic, sulphuric and phosphoric acids.

Compounds of the formula (1) may form pharmaceutically acceptable salts with metal ions, such as alkali metals for example sodium and potassium, or with an ammonium ion.

In order to use a compound of the formula (1) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of formula (1) and their pharmaceutically acceptable salts may be administered in standard manner for the treatment of the indicated diseases, for example orally, sub-lingually, parenterally, transdermally, rectally, via inhalation or via buccal administration.

Compounds of formula (1) and their pharmaceutically acceptable salts which are active when given orally or via buccal administration can be formulated as liquids, syrups, tablets, capsules and lozenges. An oral liquid formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, starch, celluloses, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil or solubilising agent, for example polyethylene glycol, polyvinylpyrrolidone, 2-pyrrolidone, cyclodextrin, lecithin, arachis oil, or sesame oil.

A typical suppository formulation comprises a compound of formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Typical compositions for inhalation ar in the form of a solution, suspension or emulsion that may be administered in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane, or are in the form of a powder for insufflation.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to himself a single dose.

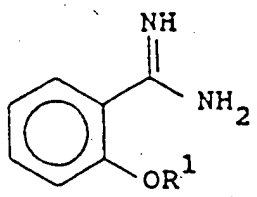
Each dosage unit for oral administration contains suitably from 0.001 mg/Kg to 30 mg/Kg, and preferably from 0.005 mg/Kg to 15 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.001 mg/Kg to 10 mg/Kg, of a compound of formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base.

The daily dosage regimen for oral administration is suitably about 0.001 mg/Kg to 120 mg/Kg, of a compound of formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, for example about 0.005 mg/Kg to 10 mg/Kg, of a compound of the formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base. The active ingredient may be administered as required for example from 1 to 8 times a day or by infusion. The compositions of the invention are bronchodilators and are useful in chronic reversible obstructive lung disease for example asthma and bronchitis. The compositions of the present invention are of use in the treatment of gastrointestinal motility disorders, such as irritable bowel syndrome. The compositions of the present invention have vasodilator activity and are of use in the treatment of angina, hypertension and congestive heart failure. Such conditions can be treated by administration orally, sub-lingually, topically, rectally, parenterally or by inhalation. For administration by inhalation dosages are controlled by a valve, are administered as required and for an adult are conveniently in the range 0.1-5.0 mg of a compound of the formula (1) or a pharmaceutically acceptable salt thereof.

The compounds of this invention may be co-administered with other pharmaceutically active compounds, for example in combination, concurrently or sequentially. Conveniently the compounds of this invention and the other active compound or compounds are formulated in a pharmaceutical composition. Examples of compounds which may be included in pharmaceutical compositions with the compounds of the formula (1) are bronchodilators such as sympathomimetic amines for example isoprenaline, isoetharine, sulbutamol, phenylephrine and ephedrine or xanthine derivatives for example theophylline and aminophylline, anti-allergic agents for example disodium cromoglycate, histamine H_1-antagonists, vasodilators for example hydralazine, angiotensin converting enzyme inhibitors for example captopril, anti-anginal agents for example isosorbide nitrate, glyceryl trinitrate and pentaerythritol tetranitrate, anti-arrhythmic agents for example quinidine, procainamide and lignocaine, calcium antagonists for example verapamil and nifedipine, diuretics such as thiazides and related compounds for example bendrofluazide, chlorothiazide, chlorothalidone, hydrochlorothiazide, and other diuretics for example frusemide and triamterene, and sedatives for example nitrazepam, flurazepam and diazepam.

In another aspect the present invention provides a process for the preparation of compounds of the formula (1) or pharmaceutically acceptable salts thereof, which process comprises :

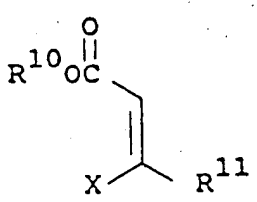
a) for compounds wherein R^2 is amino, reacting a compound of the formula (2) :



(2)

wherein R^1 is as hereinbefore defined with a C_{1-6}alkyl cyanoacetate;

b) for compounds wherein R^2 is hydroxy, phenyl, C_{1-6}alkyl or carboxy, reacting a compound of the formula (2) as hereinbefore defined with a compound of the formula (3) :



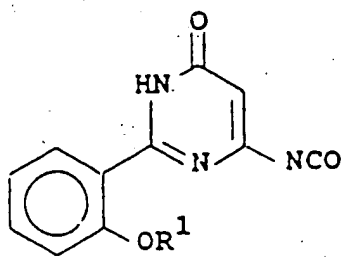
(3)

wherein X is a displaceable group, R^{11} is hydroxy, phenyl, C_{1-6}alkyl or carboxy and R^{10} is an ester forming group;

c) for compounds wherein R^2 is $-NHCOR^3$, reacting a compound of the formula (1) wherein R^2 is amino with a formylating agent or a C_{2-7}alkanoylating agent;

d) for compounds wherein R^2 is $-NHCONHR^4$ in which R^4 is C_{1-6}alkyl, reacting a compound of the formula (1) wherein R^2 is amino with a C_{1-6}alkyl isocyanate;

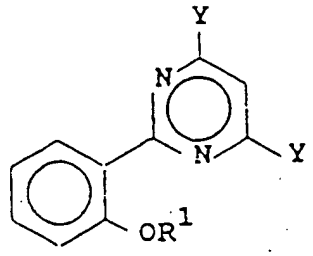
e) for compounds wherein R^2 is $-NHCONH_2$, reacting a compound of the formula (4)



(4)

wherein R^1 is as hereinbefore defined with ammonia;

f) for compounds wherein R^2 is halo, hydrolysing a compound of the formula (5) :



(5)

wherein R^1 is as hereinbefore defined and Y is halo;

g) for compounds wherein R^2 is $-NR^8R^9$, reacting a compound of the formula (1) wherein R^2 is halo with an amine HNR^8R^9 wherein R^8 and R^9 are as hereinbefore defined;

h) for compounds wherein R^2 is $-CO_2R^5$ in which R^5 is C_{1-6}alkyl, reacting a compound of the formula (1) wherein R^2 is carboxy with R^5OH in which R^5 is C_{1-6}alkyl in the presence of an acid catalyst;

i) for compounds wherein R^2 is $-CONR^6R^7$, reacting a compound of the formula (1) wherein R^2 is $-CO_2R^5$ in which R^5 is C_{1-6}alkyl with an amine HNR^6R^7 wherein R^6 and R^7 are as hereinbefore defined;

j) for compounds wherein R^2 is cyano, dehydrating a compound of the formula (1) wherein R^2 is $-CONH_2$;

k) for compounds wherein R^2 is 5-tetrazolyl, reacting a compound of the formula (1) wherein R^2 is cyano with an azide salt; or

l) for compounds wherein R^2 is C_{1-6}alkoxy, reacting a compound of the formula (1) wherein R^2 is halo with a C_{1-6}alkoxide salt; and thereafter optionally forming a pharmaceutically acceptable salt.

Suitably a compound of the formula (2) is treated with a C_{1-6}alkyl cyanoacetate such as ethyl cyanoacetate or a compound of the formula (3) in water or an organic solvent such as a C_{1-4}alkanol or dimethylformamide or mixtures thereof in the presence of a base such as sodium hydroxide, a sodium alkoxide or sodium hydride at ambient or elevated temperature, for example 40-150° C, conveniently at the reflux temperature of the reaction mixture.

Suitably X is hydroxy or a derivative thereof, for example X is protected hydroxy such as silyloxy, an acid residue (for example C_{1-6}alkanoyloxy) or an ether residue (for example methoxy or ethoxy). Suitably R^{10} is C_{1-6}alkyl, for example methyl or ethyl. Preferably when R^{11} is hydroxy, R^{10} is ethyl and X is ethoxy, that is a compound of the formula (2) is reacted with diethylmalonate. Preferably when R^{11} is methyl, ethyl or phenyl, R^{10} is ethyl and X is hydroxy, that is a compound of the formula (2) is reacted with ethyl acetoacetate, ethyl propionylacetate or ethyl benzoylacetate. Preferably when R^{11} is carboxy, R^{10} is ethyl and X is hydroxy, that is a compound of the formula (2) is reacted with ethyl 4-oxalacetate.

The reaction between a compound of the formula (1) wherein R^2 is amino and a formylating agent or a

C_{2-7}alkanoylating agent is conveniently performed in the absence of a solvent or in a suitable solvent such as a N-methylpyrrolidone or pyridine at ambient or elevated temperature, for example 50-200°C, preferably 100-150°C. Examples of formylating agents include formic acid, C_{1-4}alkyl formate or C_{1-4}alkyl formamide. Examples of C_{2-7}alkanoylating agents include acid anhydrides such as acetic, propionic, or n-butyric anhydride or acid halides such as acetyl or propionyl chloride.

The reaction between a compound of the formula (1) wherein R^2 is amino and a C_{1-6}alkyl isocyanate or the reaction between a compound of formula (4) and ammonia is conveniently performed in an organic solvent such as dioxan, toluene or a halohydrocarbon such as chloroform at ambient or elevated temperature, for example 50-150°C, preferably at the reflux temperature of the reaction mixture.

A compound of the formula (5) is suitably hydrolysed by reaction with a concentrated acid such as hydrochloric acid in an organic solvent such as a C_{1-4}alkanol. Suitably Y is chloro or bromo.

The reaction between a compound of the formula (1) wherein R^2 is halo and an amine HNR^8R^9 is suitably performed in an organic solvent such as a C_{1-4}alkanol at an elevated temperature, for example 50-120°C, conveniently in a pressure vessel.

A compound of the formula (1) wherein R^2 is carboxy is suitably reacted with an excess of R^5OH in the absence of a solvent or in the presence of an inert solvent such as toluene or a halohydrocarbon, at an elevated temperature, for example 40-120°C, preferably at the reflux temperature of the reaction mixture. A suitable acid catalyst is concentrated sulphuric acid or anhydrous hydrogen chloride.

The reaction of a compound of the formula (1) wherein R^2 is CO_2R^5 in which R^5 is C_{1-6}alkyl with HNR^6R^7 is suitably performed in water or an organic solvent such as a C_{1-4}alkanol or mixtures thereof at ambient or elevated temperature, for example 40-120°C, conveniently at the reflux temperature of the reaction mixture.

A compound of the formula (1) wherein R^2 is $-CONH_2$ is suitably reacted with a dehydrating agent such as phosphorous pentoxide, phosphoryl chloride or thionyl chloride in the absence of a solvent or in an inert organic solvent such as toluene at ambient or elevated temperature, for example 40-120°C, preferably at the reflux temperature of the reaction mixture. The reaction with phosphoryl chloride may result in the formation of an intermediate chloropyrimidine compound which is suitably hydrolysed to the desired pyrimidone by reaction with glacial acetic acid at elevated temperature, for example 40-120°C.

The reaction of a compound of the formula (1) wherein R^2 is cyano with an azide salt is suitably performed in an organic solvent such as dimethylformamide, dimethylsulfoxide, N-methylpyrrolidine-2-one or tetrahydrofuran at an elevated temperature, for example 40-200°C, preferably at the reflux temperature of the reaction mixture. Suitable azide salts include ammonium, sodium, potassium or aluminium azide.

A compound of the formula (1) wherein R^2 is halo is suitably reacted with a C_{1-6}alkoxide salt, such as an alkali metal C_{1-6}alkoxide for example sodium ethoxide or sodium methoxide in an organic solvent such as a C_{1-4}alkanol at an elevated temperature, for example 50-140°C, conveniently in a pressure vessel.

A compound of the formula (4) is suitably prepared by reacting a compound of the formula (1) wherein R^2 is amino with phosgene or a chemical equivalent thereof. Chemical equivalents of phosgene include trichloromethyl chloroformate or carbonyldiimidazole.

A compound of the formula (5) is conveniently prepared by reaction of a compound of the formula (1) wherein R^2 is hydroxy with a halogenating agent such as phosphoryl chloride, thionyl chloride or phosphorous tribromide. Alternatively a compound of the formula (1) wherein R^2 is hydroxy is converted to a tosyl derivative which is then reacted in conventional manner with a halide anion, such as fluoride, chloride, bromide or iodide to form a compound of the formula (5).

Compounds of the formula (2) are known or preparable in conventional manner from US Patent 3,819,631.

Pharmaceutically acceptable acid addition salts of the compounds of the formula (1) wherein R^2 is $-NR^8R^9$ may be prepared from the corresponding base of the compounds of the formula (1) in conventional manner. For example the base may be reacted with an acid in a C_{1-4}alkanol, or an ion-exchange resin may be used. The salts of the compounds of the formula (1) may be interconverted using ion-exchange resins. Non-pharmaceutically acceptable salts are therefore of use as they can be converted to pharmaceutically acceptable salts.

Pharmaceutically acceptable base addition salts of the compounds of the formula (1) may be prepared by standard methods, for example by reacting a solution of the compound of the formula (1) with a solution of the base.

The following biological test methods, data and Examples serve to illustrate this invention.

Bronchodilatation - In vivo

Malo guinea-pigs of the Dunkin Hartley strain (500 - 600g) were anaesthetised with Sagatal (pentobarbital sodium) (60 mg/kg). Airway resistance was measured using a modification of the classical Konzett-Rossler technique (J. Pharm. Methods, 13, 309-315, 1985). U46619 (9,11-methanoepoxy-PGH_2) was infused i.v. at a rate of 2.5 nmol/min, this produced a steady state of bronchoconstriction (approximately 120% increase from basal airway resistance). The compound under test was administered by i.v. bolus injection, and the subsequent peak inhibition of bronchoconstriction recorded.

The dose of compound required to reduce the U46619 -induced bronchoconstriction by 50% is given as the BD_{50}. These results demonstrate in vivo anti-bronchoconstrictor activity.

COMPOUND	BD_{50} (µmol/kg)
5	8.34
16	6.03
18	9.70

Phosphodiesterase activity

The activity of the compounds of the present invention as inhibitors of a caimodulin insensitive cyclic GMP phosphodiesterase was measured using the procedure described in European Patent Application No. 293063. The compounds of Examples 1 to 24 had IC_{50} values (the concentration of inhibitor required for 50% inhibition of enzyme activity) in the range 0.5 to 88 µM. The compounds of the present invention have the advantage that they are selective in not inhibiting cyclic AMP phosphodiesterase (type III).

Inhibition of spontaneous colonic activity - in vitro

Male albino guinea-pigs (300 - 400g) were killed by a blow to the back of the head and exsanguinated. A 2cm long segment of the proximal part of the hypogastric loop of the distal colon was rapidly dissected out and placed in oxygenated (95% O_2, 5% CO_2) modified warm Krebs solution. The tissue was cleaned out with Krebs and the adjoining mesentery discarded. Cotton was then tied to each end and the colon was attached to a tissue holder in an organ bath containing modified oxygenated Krebs solution at 37° C. The other end of the tissue was tied to an isometric transducer and placed under 1g tension. Force developed by the muscle was detected by the transducer, and recorded on a multitrace pen recorder. Spontaneous colonic activity, as assessed by the contraction distance over a five minute period, was subjected to computer analysis.

The tissues were allowed to settle at a resting tension of 1g for 1 hour, during which time they were washed at 15 minute intervals. Three samples of pre-dose activity were taken and averaged. The tissues were then dosed and two samples of post-dose activity were taken. The lowest value was used to calculate the percentage relaxation, and log dose response curves were constructed. The tissues were washed 10 minutes after dosing and left for 15 minutes to settle prior to the next control period.

The concentration of compound required to reduce spontaneous colonic activity by 50% is given as the IC_{50}.

COMPOUND	IC_{50} (µM)
5	2.4
15	0.75
18	3.3
21	3.7

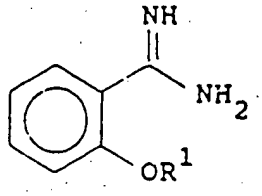
N-propyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
6-ethoxy-2-(2-propoxyphenyl)pyrimidin-4(3H)-one, or
6-N,N-bis-(2-hydroxyethyl)amino-2-(2-propoxyphenyl)pyrimidin-4(3H)-one,
or a pharmaceutically acceptable salt thereof.

12. A compound according to any one of claims 1 to 11 for use as a medicament.

13. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 11 and a pharmaceutically acceptable carrier.

14. A process for preparing a compound of the formula (1) or a pharmaceutically acceptable salt thereof as defined in claim 1 which process comprises:

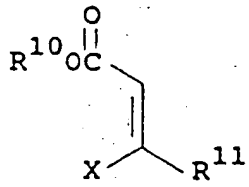
a) for compounds wherein R^2 is amino, reacting a compound of the formula (2) :



(2)

wherein R^1 is as defined in claim 1 with a C_{1-6}alkyl cyanoacetate;

b) for compounds wherein R^2 is hydroxy, phenyl, C_{1-6}alkyl or carboxy, reacting a compound of the formula (2) as hereinbefore defined with a compound of the formula (3) :



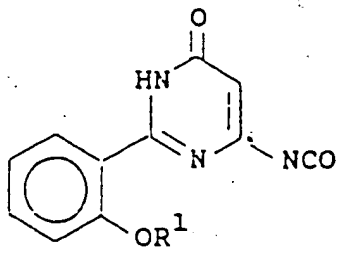
(3)

wherein X is a displaceable group, R^{11} is hydroxy, phenyl, C_{1-6}alkyl or carboxy and R^{10} is an ester forming group;

c) for compounds wherein R^2 is $-NHCOR^3$, reacting a compound of the formula (1) wherein R^2 is amino with a formylating agent or a C_{2-7}alkanoylating agent;

d) for compounds wherein R^2 is $-NHCONHR^4$ in which R^4 is C_{1-6}alkyl, reacting a compound of the formula (1) wherein R^2 is amino with a C_{1-6}alkyl isocyanate;

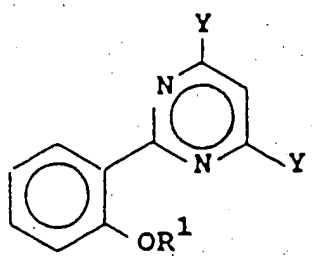
e) for compounds wherein R^2 is $-NHCONH_2$, reacting a compound of the formula (4)



(4)

wherein R^1 is as hereinbefore defined with ammonia;

f) for compounds wherein R^2 is halo, hydrolysing a compound of the formula (5) :



(5)

wherein R^1 is as hereinbefore defined and Y is halo;

g) for compounds wherein R^2 is $-NR^8R^9$, reacting a compound of the formula (1) wherein R^2 is halo with an amine HNR^8R^9 wherein R^8 and R^9 are as defined in claim 1;

h) for compounds wherein R^2 is $-CO_2R^5$ in which R^5 is C_{1-6}alkyl, reacting a compound of the formula (1) wherein R^2 is carboxy with R^5CH in which R^5 is C_{1-6}alkyl in the presence of an acid catalyst;

i) for compounds wherein R^2 is $-CONR^6R^7$, reacting a compound of the formula (1) wherein R^2 is $-CO_2R^5$ in which R^5 is C_{1-6}alkyl with an amine HNR^6R^7 wherein R^6 and R^7 are as defined in claim 1;

j) for compounds wherein R^2 is cyano, dehydrating a compound of the formula (1) wherein R^2 is $-CONH_2$;

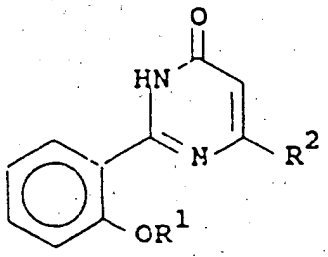
k) for compounds wherein R^2 is 5-tetrazolyl, reacting a compound of the formula (1) wherein R^2 is cyano with an azide salt; or

l) for compounds wherein R^2 is C_{1-6}alkoxy, reacting a compound of the formula (1) wherein R^2 is halo with a C_{1-6}alkoxide salt;

and thereafter optionally forming a pharmaceutically acceptable salt.

Claims for the following Contracting States: ES, GR

1. A process for preparing a compound of the formula (1) :



(1)

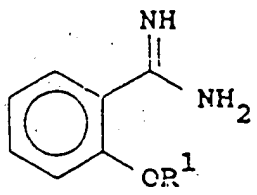
or a pharmaceutically acceptable salt thereof, wherein

R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-6}alkyl, phenylC_{1-6}alkyl or C_{1-6}alkyl substituted by 1 to 6 fluoro groups; and

R^2 is C_{1-6}alkyl, phenyl, hydroxy, C_{1-6}alkoxy, halo, $-NHCOR^3$, $-NHCONHR^4$, 5-tetrazolyl, $-CO_2R^5$, cyano, $-CONR^6R^7$, or $-NR^8R^9$ wherein R^3 to R^7 are independently hydrogen or C_{1-6}alkyl and R^8 and R^9 are independently hydrogen or C_{1-6}alkyl optionally substituted by hydroxy provided that the carbon atom adjacent to the nitrogen atom is not substituted by hydroxy;

which process comprises :

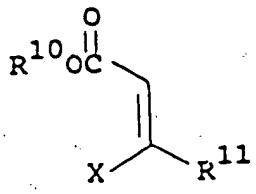
a) for compounds wherein R^2 is amino, reacting a compound of the formula (2) :



(2)

wherein R^1 is as hereinbefore defined in claim 1 with a C_{1-6}alkyl cyanoacetate;

b) for compounds wherein R^2 is hydroxy, phenyl, C_{1-6}alkyl or carboxy, reacting a compound of the formula (2) as hereinbefore defined with a compound of the formula (3) :



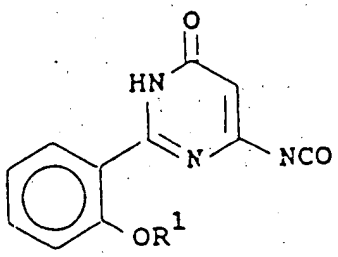
(3)

wherein X is a displaceable group, R^{11} is hydroxy, phenyl, C_{1-6}alkyl or carboxy and R^{10} is an ester forming group;

c) for compounds wherein R^2 is -NHCOR^3, reacting a compound of the formula (1) wherein R^2 is amino with a formylating agent or a C_{2-7}alkanoylating agent;

d) for compounds wherein R^2 is -NHCONHR^4 in which R^4 is C_{1-6}alkyl, reacting a compound of the formula (1) wherein R^2 is amino with a C_{1-6}alkyl isocyanate;

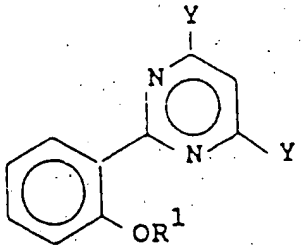
e) for compounds wherein R^2 is -NHCONH$_2$, reacting a compound of the formula (4)



(4)

wherein R^1 is as hereinbefore defined with ammonia;

f) for compounds wherein R^2 is halo, hydrolysing a compound of the formula (5) :



(5)

wherein R^1 is as hereinbefore defined and Y is halo;

g) for compounds wherein R^2 is -NR^{8}R^9, reacting a compound of the formula (1) wherein R^2 is halo with an amine HNR^{8}R^9 wherein R^8 and R^9 are as hereinbefore defined in claim 1;

h) for compounds wherein R^2 is -CO$_2$R^5 in which R^5 is C_{1-6}alkyl, reacting a compound of the formula (1) wherein R^2 is carboxy with R^{5}OH in which R^5 is C_{1-6}alkyl in the presence of an acid catalyst;

i) for compounds wherein R^2 is -CONR^{6}R^7, reacting a compound of the formula (1) wherein R^2 is -CO$_2$R^5 in which R^5 is C_{1-6}alkyl with an amine HNR^{6}R^7 wherein R^6 and R^7 are as hereinbefore defined in claim 1;

j) for compounds wherein R^2 is cyano, dehydrating a compound of the formula (1), wherein R^2 is -CONH$_2$;

k) for compounds wherein R^2 is 5-tetrazolyl, reacting a compound of the formula (1) wherein R^2 is cyano with an azide salt; or

l) for compounds wherein R^2 is C_{1-6}alkoxy, reacting a compound of the formula (1) wherein R^2 is halo with a C_{1-6}alkoxide salt;

and thereafter optionally forming a pharmaceutically acceptable salt.

2. A process according to claim 1 wherein R^1 is C_{2-5}alkyl.

3. A process according to claim 1 wherein R^1 is C_{3-5}alkenyl.

4. A process according to claim 1 wherein R^1 is n-propyl.

5. A process according to any one of claims 1 to 4 wherein R^2 is phenyl or C_{1-6}alkyl.

6. A process according to any one of claims 1 to 4 wherein R^2 is hydroxy, C_{1-6}alkoxy or halo.

7. A process according to any one of claims 1 to 4 wherein R^2 is $-NHCOR^3$ or $-NHCONHR^4$.

8. A process according to any one of claims 1 to 4 wherein R^2 is 5-tetrazolyl or $-CO_2R^5$.

9. A process according to any one of claims 1 to 4 wherein R^2 is cyano or $-CONR^6R^7$.

10. A process according to any one of claims 1 to 4 wherein R^2 is $-NR^8R^9$.

11. A process according to claim 1 for preparing a compound which is :

6-amino-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-acetamido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-propionamido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-butyramido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-N'-methylureido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
4,6-dihydroxy-2-(2-propoxyphenyl)pyrimidine,
4-chloro-6-hydroxy-2-(2-propoxyphenyl)pyrimidine,
6-ethylamino-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-propylamino-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-(2-hydroxyethylamino)-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-(3-hydroxypropylamino)-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
4-hydroxy-6-methyl-2-(2-propoxyphenyl)pyrimidine,
6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxylic acid,
ethyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxylate,
6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
4-cyano-6-hydroxy-2-(2-propoxyphenyl)pyrimidine,
2-(2-propoxyphenyl)-6-(1H-tetrazol-5-yl)pyrimidin-4(3H)-one,
4-ethyl-6-hydroxy-2-(2-propoxyphenyl)pyrimidine,
4-hydroxy-6-phenyl-2-(2-propoxyphenyl)pyrimidine,
N-methyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
N-ethyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
N-propyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
6-ethoxy-2-(2-propoxyphenyl)pyrimidin-4(3H)-one, or
6-N,N-bis-(2-hydroxyethyl)amino-2-(2-propoxyphenyl)pyrimidin-4(3H)-one,
or a pharmaceutically acceptable salt thereof.

12. A process for preparing a pharmaceutical composition which comprises bringing into association a compound according to any one of claims 1 to 11 and a pharmaceutically acceptable carrier.